Abdominal aorta aneurysm: an exceptional expression of atherosclerotic disease in type II diabetes

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Online publish-ahead-of-print 12 February 2008

This editorial refers to ‘Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte–matrix interactions’ by J. Golledge et al.,1 on page 665

An aortic abdominal aneurysm (AAA) is a potentially lethal disease. In a population with one or multiple cardiovascular risk factors, its prevalence is estimated at 1.6% (aneurysm size >3 cm) and 0.5% (aneurysm size >4 cm), with a higher occurrence in male vs. female patients. In the presence of type II diabetes, the prevalence of all cardiovascular disease (including carotid stenosis, AAA, and peripheral artery disease) is doubled.1 The Veterans Affairs Cooperative Study Investigators study showed a higher prevalence of AAA in their screened population. In addition, a negative association was found between AAA and the presence of diabetes (with no difference in male vs. female).2 Despite the fact that AAA is an expression of atherosclerotic disease (with a large amount of pro-inflammation), the prevalence of AAA in diabetic patients is less than expected. In other words, AAA in diabetes is a non-frequent macrovascular complication related to atherosclerotic disease. Such a conclusion appears quite remarkable; previously, it has been stated that the AAA expansion rate in diabetes is delayed compared with non-diabetic patients. However, these differences in expansion rate between smaller and larger AAAs were not seen in diabetic subjects.5 Despite a reduced prevalence of AAA in diabetic patients, co-existence of diabetes has been associated with a decreased 2.5-year survival due to co-existing atherothrombotic coronary disease.6 Taken together, these observations show that the AAA expansion rate in diabetes is delayed compared with non-diabetic patients. Therefore, a small AAA in diabetic patients will probably not reach >5 cm in size within a 5 year interval, which is an indicator of the need for surgical repair.

In their report, Golledge et al. found that patients with diabetes, after adjusting for smoking history and co-existence of peripheral arterial disease, had an odds ratio of 0.18 [0.06–0.57; 95% confidence interval (CI)] of experiencing above median growth compared with those in the non-diabetic cohort (even after including dyslipidaemia and glucose). In addition, no statistical association was found for serum glucose levels and a marker for advanced glycation, Ne-carboxymethyl lysine (CML). Unfortunately, Golledge et al. could not show blood glycated haemoglobin (HbA1c), a well-known marker that reflects average glucose burden. These observations are quite surprising and may have clinical importance;
should clinicians focus on strict glucose control to prevent AAA expansion in diabetes? In accordance with Golledge et al., the answer will be negative. Factors other than glucose, either in circulation or in local vascular tissue, are probably more important in AAA expansion. Despite their conclusion derived from human observation, Golledge et al. hypothesized that high levels of glucose in local vascular tissue were responsible for increased glycation of the main components in the extracellular matrix (ECM) within the abdominal aorta wall. These alterations in ECM composition may prevent excessive proteolysis by locally released metalloproteinases (MMP-2 and MMP-9) with, in parallel, secretion of the pro-inflammatory cytokine interleukin-6 (IL-6). Both MMPs play a key role in formation and progression of AAA. Previously, other studies showed that inhibition of MMPs with doxycyclin (phase II study) or simvastatin (40 mg daily for 3 weeks prior to elective surgery) results in a delay in AAA growth.

Furthermore, gene disruption of both MMPs in a rodent model prevents development of AAA. Golledge and co-workers support these observations as they showed that both glycation and cross-linking of collagen lattices resulted in a decreased MMP activity (as measured by gel zymography). This reduction in MMP activity could lead in vivo to a decline in aortic media destruction with a delay in AAA expansion. Since plasma levels of MMP have been shown to be elevated in patients with AAA, comparison of MMP levels between diabetic and non-diabetic AAA patients in Golledge’s study could have strengthened their hypothesis. Another important factor that is related to AAA progression is c-Jun N-terminal kinase (JNK). Inhibition of this factor results in AAA regression. IL-6 increases expression of JNK. Golledge et al. found that monocytes that were exposed to glycated and cross-linked collagen lattices produced less IL-6 (compared with monocytes that were exposed to normal collagen lattices). Therefore, in summary, glycation of the ECM results in a decreased MMP activity with subsequent reduction of ECM breakdown and decreased IL-6 production, leading to inhibition of JNK. Another mechanism to explain a reduced AAA growth in diabetes was recently proposed by Astrand et al. who found less aortic wall stress in diabetic patients compared with non-diabetic patients due to a thicker aortic wall (measured by intima-media thickness from the abdominal aorta). Without any doubt, other local factors could also be additional players in the formation of AAA in diabetes, such as impaired function of smooth muscle cells and immune cells due to glucotoxicity.

All these observations regarding AAA in diabetes could teach us several important lessons regarding atherosclerotic disease, such as the heterogeneous expression in different arteries (coronary artery vs. abdominal artery vs. cerebral artery) and the key role of local proteolytic enzymes (such as MMPs) in pro-inflammatory cascades and atherogenesis. Better understanding of these marked local differences within atherosclerotic vascular tissue in diabetes may give us more insight into local atherogenesis with a perspective for future therapeutic approaches.

Acknowledgement

The work of Th. B. Twickler is supported by a grant of the Netherlands Organization of Science (NWO).

Conflict of interest: none declared.

References